

## **REMARKS/ARGUMENTS**

The foregoing amendments in the claims are of a formal nature, and do not add new matter. Applicants believe that the current amendments place all claims in *prima facie* condition for allowance or, at least, in a better form for consideration on appeal. Accordingly, the consideration and entry of the present amendment after final rejection is respectfully requested.

Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional, or continuation-in-part applications.

Claims 33, 38-40, and 44-47 are pending in this application.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, second paragraph, 35 U.S.C. §102(e), and 35 U.S.C. §112, first paragraph, for lack of written description.

The remaining objections and rejections of Claims 32, 33, 38, and 44-47 under 35 U.S.C. §101 and under 35 U.S.C. §112, first paragraph, for lack of enablement, are addressed below.

### **I. Information Disclosure Statement**

Applicants respectfully thank the Examiner for considering the supplemental Information Disclosure Statement filed on February 3, 2005.

### **II. Claim Objections**

Claim 33 is objected to because the phrase "shown in" in part (a) should be deleted. Applicants have deleted the recitation of "shown in" from Claim 33 by the amendment herein.

Claim 38 is objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner states that "[c]laim 38 recites the isolated nucleic acid of claim 33 comprising the nucleic acid sequence of SEQ ID NO:373. However, claim 33 also recites an isolated nucleic acid comprising the nucleic acid sequence of SEQ ID NO:373."

Applicants respectfully submit that Claim 33 recites additional subject matter not recited in Claim 38. Part (b) of Claim 38 recites "the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:373" while part (c) recites "the full-length coding sequence of the cDNA deposited under ATCC accession number 203465." Because this additional subject

matter is not recited in Claim 38, Claim 38 further limits the subject matter of Claim 33, and thus is a proper dependent claim.

Accordingly, withdrawal of the claim objections is respectfully requested.

### **III. Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph (Enablement)**

Claims 33, 38-40, and 44-47 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." (Page 3 of the instant Office Action). The Examiner alleges that "[f]urther research needs to be done to determine whether the small increase in PRO1759 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial" (Page 6 of the instant Office Action).

Claims 33, 38-40, and 44-47 further remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility one skilled in the art clearly would not know how to use the invention." (Page 10 of the instant Office Action).

Applicants respectfully disagree and traverse the rejections.

Applicants submit, for the reasons set forth below, that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1759 polynucleotides.

#### **Utility – Legal Standard**

According to 35 U.S.C. § 101:

Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*<sup>1</sup> the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or

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<sup>1</sup> *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

her invention, i.e. a utility "where specific benefit exists in currently available form."<sup>2</sup> The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."<sup>3</sup>

Later, in *Nelson v. Bowler*<sup>4</sup> the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."<sup>5</sup> In *Cross v. Iizuka*<sup>6</sup> the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."<sup>7</sup> The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."<sup>8</sup>

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.<sup>9</sup> The PTO has the initial

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<sup>2</sup> *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

<sup>3</sup> *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

<sup>4</sup> *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

<sup>5</sup> *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

<sup>6</sup> *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

<sup>7</sup> *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

<sup>8</sup> *Id.*

<sup>9</sup> *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

burden that applicants' claims of usefulness are not believable on their face.<sup>10</sup> In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."<sup>11</sup>,<sup>12</sup>

Compliance with 35 U.S.C. §101 is a question of fact.<sup>13</sup> The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.<sup>14</sup> Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")<sup>15</sup>, which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

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<sup>10</sup> *Ibid.*

<sup>11</sup> *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

<sup>12</sup> See also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

<sup>13</sup> *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

<sup>14</sup> *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

<sup>15</sup> 66 Fed. Reg. 1092 (2001).

In explaining the “substantial utility” standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a ““substantial”” utility.”<sup>16</sup> Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,<sup>17</sup> gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

#### **Utility – Application of Standard**

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the claimed polynucleotides for the reasons previously set forth in the Applicants' response filed on February 3, 2005, and below.

The Examiner acknowledges that "the specification provides data showing that polynucleotides encoding PRO1759 are more highly expressed in lung and colon tumor tissue as compared to normal lung and colon tissue." The Examiner asserts, however, that "there is no further supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the claimed invention is also differentially expressed in the tumor tissue as compared to the normal tissue, and as such, one of skill in the art would conclude that it is not supported by a substantial asserted utility or a well-established utility." The Examiner concludes that "[u]tility of a novel nucleic acid involved in cancer will depend upon the role that the expressed polypeptide plays in cancer initiation, progression, growth, maintenance, etc." (Pages 4-5 of the instant Office Action).

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<sup>16</sup> M.P.E.P. §2107.01.

<sup>17</sup> M.P.E.P. §2107 II (B)(1).

Applicants respectfully point out that the utility of a polynucleotide does not depend upon the function of the encoded protein. A polynucleotide may have utility, for example, as a disease marker. As in this instance, a polynucleotide that is overexpressed in a particular disease, such as lung or colon cancer, has utility as a marker for diagnosis of this disease. One of ordinary skill in the art would readily understand how to use a polynucleotide that is overexpressed in lung and colon tumors for the diagnosis of lung and colon cancer without necessarily knowing the function of the encoded protein. The correlation between overexpression of the polynucleotide and cancer is sufficient.

Given that it is overexpression of the encoding polynucleotide that is used to diagnose lung or colon cancer, it is not necessary to determine the expression levels of the encoded protein in lung or colon tumors. The utility of the claimed polynucleotide sequences depends upon polynucleotide expression levels, not protein expression levels. For this reason, the discussion regarding correlation between mRNA and protein levels (see pages 5-6 of the instant Office Action) is irrelevant.

The Examiner alleges that “the specification’s assertions that the claimed PRO1759 polynucleotides encoding the polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.” (See page 6 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

As stated above, in explaining the “substantial utility” standard, M.P.E.P. §2107.01 cautions that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement<sup>18</sup> states, “If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

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<sup>18</sup> M.P.E.P. §2107 II (B)(1).

Applicants respectfully submit that the specification discloses that the nucleic acids encoding PRO1759 had  $\Delta Ct$  value of > 1.0, which is **more than a 2-fold increase**, in at least three lung and colon tumors (HF-000840, HF-000795 and HF-001296).

Applicants further submitted the Declaration by Audrey Goddard, Ph.D. which clearly establishes that the TaqMan realtime PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy and is in extensive use for the study of gene amplification. Dr. Goddard in her Declaration confirms that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) is significant and useful. The Goddard Declaration further confirms that based on the gene amplification results set forth in Table 8, one of ordinary skill would find it credible that a 2-fold increase in gene copy number (as seen with PRO1759) would indicate that the gene is a diagnostic marker of human lung and colon cancer.

Applicants also submitted the Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and a Director of the Molecular Oncology Department at Genentech, Inc., the assignee of the present application. In his Declaration, Dr. Ashkenazi states, "Even in the absence of overexpression of the gene product, amplification of a cancer marker gene - as detected, for example, by the reverse transcriptase TaqMan PCR or the fluorescence *in situ* hybridization (FISH) assays - is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy."

Accordingly, Applicants respectfully submit that Applicants' assertion that the asserted utility for the PRO1759 polynucleotides, for example in the detection of lung and colon cancer, is substantial.

The Examiner states that the declarations of Dr. Goddard and Dr. Ashkenazi, as relied upon in Applicants' arguments, have not been considered because they allegedly were not submitted with the Response to Office Action filed February 3, 2005. Applicants have attached a copy of the return postcard stamped by the Patent Office indicating receipt of the Amendment and Response to Office Action, as well as the Declarations of Audrey D. Goddard and Avi Ashkenazi, on February 3, 2005. Accordingly, the Declarations of Dr. Goddard and Dr. Ashkenazi should be considered.

The Examiner further contends that even if the declarations of Dr. Goddard and Dr. Ashkenazi were filed under 37 CFR 1.132, they would be insufficient to overcome the rejection of claims 28-35 and 38-40 based upon 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. (See page 7 of the instant Office Action). The Examiner further asserts that "all that the specification does is present evidence that the DNA encoding PRO1759 is amplified in a variety of samples and invites the artisan to determine the significance of this increase." (See page 7 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

Applicants have submitted Dr. Goddard's Declaration to show that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1759 is a diagnostic marker of lung and colon cancer.

The Examiner asserts that "[t]he PRO1759 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1759 nucleic acid was amplified in two cancer samples, to a minor degree (about 2.5 fold)." (Page 7 of the instant Office Action). The Examiner further asserts that "Applicant's arguments do not provide data such that the examiner can independently draw conclusions." (Page 8 of the instant Office Action).

Applicants first note that the PRO1759 nucleic acid was amplified in three cancer samples, as shown in Table 8. Applicants next emphasize that the opinions expressed in the Goddard Declaration are all based on factual findings. Thus, Dr. Goddard explains that the TaqMan PCR assay is based on the principle that successful PCR yields a fluorescent signal due to Taq DNA polymerase-mediated exonuclease digestion of a fluorescently labeled oligonucleotide that is homologous to a sequence between two PCR primers. Further, Dr. Goddard explains that the assay is extremely sensitive technique which leads to accurate determination of gene copy number. Dr. Goddard adds that the TaqMan PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression. For support, Dr. Goddard cites a number of references including a publication by

Pennica *et al.* in which Dr. Goddard is a co-author of the paper. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Goddard would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.<sup>19</sup> "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"<sup>20</sup> Furthermore, the Federal Court of Appeals held in *In re Alton*, "[w]e are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"<sup>21</sup>. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines<sup>22</sup> which states that, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Goddard Declaration) states that "a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy." Therefore, barring evidence to the contrary regarding the above statement in the Goddard Declaration, this rejection is improper under both the case law and the Utility guidelines.

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<sup>19</sup> *In re Rinehart*, 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki*, 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

<sup>20</sup>. *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

<sup>21</sup> *In re Alton*, *supra*.

<sup>22</sup> Part IIB, 66 Fed. Reg. 1098 (2001).

The Examiner cites Hu *et al.* in support of the assertion that "the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue." (Page 8 of the instant Office Action). The Examiner states that Hu *et al.* discloses that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease.

First of all, Applicants respectfully submit that the present application is directed to the nucleic acid sequence of SEQ ID NO:276 which encodes the PRO1317 polypeptide. Therefore, Applicants fail to see the relevance of the Examiner's rejections for lack of utility in the instant Office Action that are directed to the alleged lack of utility for the PRO1317 polypeptide.

Nevertheless, Applicants respectfully submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Accordingly, contrary to the Examiner's assertion, Applicants respectfully submit that Hu *et al.* does not conclusively show that it is more likely than not that the gene amplification does not result in increased expression at the mRNA and polypeptide levels.

First, the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based a statistical analysis of the information disclosed in published literature. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships." In particular, Hu *et al.* relied on MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column).

Therefore, Applicants submit that the reference by Hu *et al.* only studies the statistical analysis of micro-array data and not the gene amplification data. Hence, their findings would not

be directly applicable to the gene amplification data. In addition, the Hu *et al.* reference does not show a lack of correlation between microarray data and the biological significance of cancer genes.

Further, the analysis by Hu *et al.* has certain statistical flaws. According to Hu *et al.*, "different statistical methods" were applied to "estimate the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (Emphasis added). Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules were overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusion based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-

positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, *let alone* the various other types of cancer genes in general. In fact, even Hu *et al.* admit that "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added).

Accordingly, Applicants respectfully submit that the Examiner has not shown that a lack of correlation between microarray data and the biological significance of cancer genes.

Furthermore, Applicants have submitted Dr. Ashkenazi's Declaration to show that even in the absence of overexpression of the gene product, amplification of a cancer marker gene is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy.

With respect to the Ashkenazi Declaration, the Examiner refers to the discussion of gene product expression in paragraph 6 of the Declaration, and agrees that "evidence regarding lack of over-expression would be useful. The Examiner asserts, however, that "there is no evidence as to whether the gene products (such as the PRO1759 polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial." (Page 9 of the instant Office Action).

Applicants respectfully point out that paragraph 6 of the Ashkenazi Declaration considers whether gene amplification data are sufficient "to provide utility for the gene product (the encoded polypeptide)." The instant claims, however, are directed to polynucleotides, not polypeptides. In paragraph 5 of his Declaration, Dr. Ashkenazi states, "Even in the absence of overexpression of the gene product, amplification of a cancer marker gene - as detected, for example, by the reverse transcriptase TaqMan PCR or the fluorescence *in situ* hybridization (FISH) assays - is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy." Accordingly, one of ordinary skill in the art would

not doubt that the amplified polynucleotides themselves have utility.

The Examiner asserts that " a slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the tissue is aneuploid. Because aneuploid DNA can be found in normal tissues or cells (see Fleischacker *et al.* and Hittleman *et al.*), detection of increased DNA copy number does not necessarily mean those cells containing the DNA are cancerous." (Page 10 of the instant Office Action).

Applicants first respectfully submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration,

An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants respectfully submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

Second, Applicants respectfully submit that Hittleman and Fleischhacker *et al.* do not disclose aneuploid DNA in "normal" tissue or cells, but in tissue that has been damaged by carcinogenic agents and is closely associated with tumorous tissue.

Applicants note that the title of the Hittleman paper is "Genetic Instabilities in Epithelial Tissues at Risk for Cancer." Hittleman studied lung tissue from chronic smokers, which had been exposed for years to carcinogenic tobacco smoke. As Hittleman explains, "[t]umors of the aerodigestive tract have been proposed to reflect a 'field cancerization' process whereby the whole tissue is exposed to carcinogenic insult (e.g., tobacco smoke) and is at increased risk for multistep tumor development (page 3). The detection of increases in chromosome number therefore identifies cells which have begun the first steps in this multistep progression to cancer. Even if these particular epithelial regions are not yet cancerous, their presence is strongly correlated with the development of cancer in the target tissue as a whole. Accordingly,

Hittleman concludes that "the measurement of chromosome instability in the target tissue will be useful in assessing cancer risk as well as response to intervention" (page 10).

The Fleischhacker *et al.* paper presents a similar situation, in which pre-cancerous tissues having increased chromosome number are strongly correlated with cancer in the overall target tissue. Fleischhacker *et al.* studied colon samples that were themselves morphologically normal, but were derived from patients with colon cancer. Fleischhacker *et al.* suggest that "individuals with colon cancer may have morphologically normal colonic tissue, which is genetically abnormal, and this abnormality may precede the development of mutations in K-ras." (Abstract).

Accordingly, both Hittleman and Fleischhacker *et al.*, show that an increase in chromosome number or gene amplification is associated not with normal tissues, but with cancerous, or pre-cancerous tissues, and therefore, increase in chromosome number or gene amplification is useful as a marker for a cancerous or pre-cancerous state. Detection of pre-cancerous cells or tissues is useful because, as explained by Hittleman, it allows for assessing cancer risk, as well as response to intervention. Hence, Applicants respectfully submit that whether a pre-cancerous or tumor sample were analyzed, the showing of DNA amplification of PRO1759 gene would still be significant, since it would lead to the diagnosis of either a pre-cancerous state or a cancerous state, which is the utility asserted here.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1759 gene. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polynucleotides.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1759 polynucleotide. Accordingly, the Examiner is requested to reconsider and withdraw the present rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

### CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (referencing Attorney's Docket No. 39780-2830 P1C65)

Respectfully submitted,

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